(12) PATENT APPLICATION **(11)** Application No. **AU 200157788 A1**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Improvements in effervescent tablet manufacture

(51)[7] International Patent Classification(s)
A61K 009/46

(21) Application No: **200157788** (22) Application Date: **2001.08.03**

(30) Priority Data

(31) Number	(32) Date	(33) Country
PQ9401	2000.08.14	AU
PQ9402	2000.08.14	AU
PQ9403	2000.08.14	AU

(43) Publication Date : **2002.02.21**
(43) Publication Journal Date : **2002.02.21**

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ABSTRACT

An effervescent tablet formulation comprising an effervescent tablet base in combination with a therapeutic or dietary substance or composition selected from the group including Cranberry extract, a Glucosamine salt, and a combination of Ubidecarenone and a Carnitine salt. A method of manufacture of such formulations is also disclosed.

AUSTRALIA

Patents Act 1990

COMPLETE SPECIFICATION

FOR A STANDARD PATENT

ORIGINAL

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Invention Title:	Improvements in Effervescent Tablet Manufacture
Details of Associated Provisional Applications:	PQ9401 filed on 14 August 2000 PQ9402 filed on 14 August 2000 PQ9403 filed on 14 August 2000

The following statement is a full description of this invention, including the best method of performing it known to us:

FIELD OF THE INVENTION

This invention relates to improvements in the manufacture of effervescent tablets. More specifically, this invention relates to an improved formulation for a tablet base that permits the manufacture of effervescent tablets in a normal or ambient environment, at the same time resulting in tablets that are less affected by atmospheric humidity.

This invention also relates to a method or process for manufacturing this base for effervescent tablets.

Further, this invention relates to the manufacture of effervescent tablets utilising this base, but further containing of number of therapeutic substances of natural origin in a normal or ambient environment. These therapeutic substances of natural origin include but are not limited to: a Cranberry Extract; a Glucosamine salt; and to Ubidecarenone plus a Carnitine salt, in combination.

BACKGROUND OF THE INVENTION

Effervescent tablets differ from normal tablets in that they are designed to be dissolved in a glass of cool water before the resulting solution is swallowed, whereas normal tablets are intended to be swallowed whole so that they disintegrate in the stomach where the temperature is approximately 37°C. It is therefore desirable that effervescent tablets have a pleasant taste.

Effervescence is achieved by including one or more weak acids, for example citric acid and/or tartaric acid and also one or more effervescing alkalis, for example sodium bicarbonate, potassium bicarbonate and/or calcium carbonate in the formulation.

In the presence of traces of water, reaction takes place between these ingredients, liberating carbon dioxide, the "effervescence". Also, water is generated by this reaction which then continues until all of one or both of the effervescing ingredients in the tablet have reacted.

Unless precautions are taken to provide a barrier between the acid(s) and alkali(s) in each tablet during manufacture, packaging and storage, atmospheric humidity alone can provide sufficient water to start this reaction. When this occurs, tablets become soft and swell up because of both the absorbed carbon dioxide and the absorbed water.

To minimise this problem, it has been a traditional practice to separately pre-dry all of the ingredients in an effervescent tablet formula to remove adsorbed moisture and then to continue the process of mixing and compressing the powders into tablets in a controlled environment in which the relative humidity of the air is less than ten percent.

There are two distinct disadvantages in this situation, namely that the investment to provide this controlled environment is substantial and further that the low moisture content inhibits the compression step. At least two percent moisture is usually required to enable powders to be compressed into a firm tablet.

Further, it has often been necessary for effervescent tablets made by conventional procedures to individually wrap each tablet to prevent dissolution from commencing due to moisture from the atmosphere.

OBJECTS OF THE INVENTION

It is an object of this invention to provide an effervescent tablet base and a method or process of manufacturing same which goes a long way towards overcoming or at least minimising the prior art problems or limitations outlined above, or of providing a clear alternative choice for consumers or manufacturers.

It is another object of this invention to provide an effervescent tablet base, and a method or process of manufacturing the same, which is relatively stable under normal or ambient conditions.

It is a further object of this invention to provide effervescent tablet formulations comprising an effervescent tablet base in combination with a therapeutic or dietary substance or composition, and a method or process of manufacturing same, wherein the therapeutic or dietary substance is selected from, but is not limited to, one or more of: a Cranberry extract; a Glucosamine salt; and a combination of Ubidecarenone and a Carnitine salt.

It is yet another object of this invention to provide an effervescent tablet formulation, where the manufacture thereof is possible in an environment wherein no special precautions have been taken to minimise the relative humidity of the air during the processing and packaging thereof.

It is yet a further object of this invention to provide a tablet formulation that requires limited protection from atmospheric moisture during subsequent storage, or packaging and storage both before and after sale.

These and other objects of this invention will become more apparent from the following description.

SUMMARY OF THIS INVENTION

According to one aspect of the invention, there is provided an effervescent tablet-base composition, which includes one or more acids (e.g. citric acid or tartaric acid) and one or more effervescing alkalis (e.g. sodium bicarbonate, potassium bicarbonate or calcium carbonate) amongst the ingredients of the tablet base, wherein the acid component of the tablet base has been pre-coated with a protective layer of a polydimethylsiloxane which substantially

minimises contact between the acid and atmospheric moisture until the tablet is purposely mixed with water.

According to another aspect of the invention, there is provided a method of preparation of an effervescent tablet base composition, wherein the acid or other effervescing components are pre-coated with a polydimethylsiloxane before the coated component is further mixed with the other tablet base ingredients.

According to a further aspect of the invention, there is provided an effervescent medicinal or therapeutic composition, and especially an effervescent tablet composition or formulation, comprising a dietary or therapeutically effective amount of a natural compound or composition selected from, but not limited to, Cranberry Extract; a Glucosamine salt; and/or a combination of Ubidecarenone and a Carnitine salt. More specifically and preferably, there is provided:-

(i) an effervescent cranberry extract composition, and especially an effervescent tablet composition or formulation, which includes a cranberry fruit extract, an acid (e.g. citric acid or tartaric acid) and an effervescing alkali (e.g. sodium bicarbonate) amongst the active ingredients of the composition, wherein the acid component of the composition has been pre-coated with a protective layer of a polydimethylsiloxane which substantially minimises contact between the acid and atmospheric moisture until the composition is purposely mixed with water;

(ii) an effervescent glucosamine composition, and especially an effervescent tablet composition or formulation, which includes a glucosamine salt, an acid (e.g. citric acid or tartaric acid) and an effervescing alkali (e.g. sodium bicarbonate) amongst the active ingredients of the composition, wherein the acid component of the composition has been pre-coated with a protective layer of a polydimethylsiloxane which substantially minimises contact between the acid and atmospheric moisture until the composition is purposely mixed with water; and

(iii) an effervescent CoEnzyme Q10 and Carnitine composition, and especially an effervescent tablet composition or formulation, which includes both CoEnzyme Q10 and Carnitine, an acid (e.g. citric acid or tartaric acid) and an effervescing alkali (e.g. sodium bicarbonate) amongst the active ingredients of the composition, wherein the acid component of the composition has been pre-coated with a protective layer of a polydimethylsiloxane which substantially minimises contact between the acid and atmospheric moisture until the composition is purposely mixed with water.

According to yet another aspect of the invention, there is provided a method of preparation of an effervescent dietary, medicinal or therapeutic composition comprising a dietary-, medicinally- or therapeutically-effective amount of a natural compound or composition selected from, but not limited to, Cranberry Extract; a Glucosamine salt; and/or a combination of Ubidecarenone and a Carnitine salt, wherein the acid or other effervescing components are pre-coated with a polydimethylsiloxane before the coated component is further mixed with the other composition ingredients.

DETAILED DESCRIPTION

a) The Effervescent Tablet Base

According to the invention the acid component of the base is pre-coated with a polydimethylsiloxane compound that effectively forms a barrier between the acids and the alkalis when only small quantities of water, from the atmosphere, are present. This enables processing of the powders into a tablet without the need to pre-dry any of the ingredients. It also largely removes the necessity of providing a special controlled environment for these operations, with considerable savings in investment.

Preferably, the polydimethylsiloxane compound has a pH similar to that of the acid components, typically pH 2-3 and preferably the concentration of the

polydimethylsiloxane is in the range 0.5 to about 1.5 per cent of the total weight of the composition.

Stability studies on batches of tablets made according to this invention have demonstrated that special precautions to protect the tablets from the atmosphere during subsequent storage, packaging and distribution are not necessary.

Preferably, according to the invention, the effervescent acid is loaded into the mixing bowl of a granulating machine fitted with a two-speed planetary mixing blade and with a separate horizontally mounted high speed chopper mixer. The polydimethylsiloxane is added and the conventional mixing blade is switched on, with high speed being selected. Mixing continues until all of the acid has been coated with this material and a damp, solid mass has been formed. After this has been achieved, the chopper mixer of the machine is switched on and the mass is subjected to this treatment for about 0.5 to 1.0 minutes, followed by a further 2 to 5 minutes of high speed mixing by the planetary blade.

The mixture is then discharged from the mixer onto stainless steel trays in thin layers. These trays are then loaded into a drying oven pre-heated to and set at 50 degrees Celsius for about 18 hours to dry.

According to one embodiment using citric acid and using a Karl Fischer Titrator apparatus, the maximum water content of the dried, coated citric acid is 0.2% w/w.

This dried, coated citric acid is then loaded into a mixing machine where it is blended with the other ingredients of the base mixture, including the effervescing alkali, for about 3 to 5 minutes.

An example of a non-limiting composition of the base mixture according to the invention is as follows:

Ingredient		Weight (mg)
Citric acid		1000
Sodium Bicarbonate		800
Calcium Carbonate		100
Polydimethylsiloxane		20
Lactose		1400 – 1475
Flavour, Powdered		35-85
Sucralose Powder		8-12
Fumaric Acid		50-80
Polyethylene Glycol 6000		50-80
	about	3600

An effervescent tablet made according to this embodiment of the invention typically has a total weight of about 4,000 mg to 4,200 milligrams so that this base formula provides the opportunity to include 500 mg or more of one or more therapeutic substances of natural origin in each tablet.

b) **Effervescent Cranberry Extract Tablets**

Typically, cranberry fruit extract is a twenty five-fold concentrate of Cranberry Juice, absorbed onto an inert solid, for example Maltodextrin. A typical specification for this concentrate is:

Appearance : A fine powder, bright pink in colour, with a faint odour and a bitter taste of cranberries. Soluble in water to form a clear pink-red solution.

Typical analysis of active constituents:

Quinic Acid	11-12% w/w
Malic Acid	8-9% w/w
Citric Acid	10-12% w/w
Anthocyanins	5-6% w/w

This invention permits the manufacture of effervescent tablets containing a relatively high dosage (200 mg) of this extract of cranberries that dissolves in a glass of relatively cool water to provide a palatable solution. This drink presents this dose of cranberries for rapid absorption of its therapeutically active ingredients from the stomach.

Cranberries have long been a popular berry fruit, known for their tangy but pleasant taste. They provide a potent source of important organic acids, including a good source of Vitamin C. However, now the common cranberry is considered very useful in promoting urinary health, providing one of Nature's best defences against cystitis and urinary tract infection. In fact, the U.S. Pharmacopoeia cites cranberry juice as an effective solution to this health problem. Recent studies have suggested that the organic acids in cranberries work by preventing bacteria from attaching to the wall of the bladder, helping to flush them out before they cause problems.

As early as the 1840s, German researchers were examining the connection between European species of cranberries and urinary tract infections. They found that the urine of people who ate cranberries contained a chemical called hippuric acid. By the turn of the century, U.S. researchers were speculating that this attribute meant that cranberries could acidify urine and thereby prevent infection. By the 1960s, however, the idea of using cranberry to treat such infections had fallen from favour because researchers failed to show that it increased urine acidity enough to prevent illness.

Today, researchers are again addressing the relationship between cranberries and a healthy urinary tract, only this time they are focussing on a different action: cranberry's potential to keep bacteria from attaching to urinary tract walls.

Urinary tract infections are generally divided into three categories:

Urethritis is an infection of the urethra, the canal that transports urine from the bladder and in males also serves as a genital duct. The infection is usually caused by viruses transmitted during intercourse. Cranberry cannot be used to prevent or treat this condition because it is not effective against viral infections.

Cystitis is an infection of the urinary bladder, the organ that stores urine, while polynephritis, or kidney infection, results when the bacteria in the bladder migrate to the kidneys. The last-mentioned type of infection is the most serious and is often accompanied by fever, chills, nausea and severe back pain. Current cranberry research is focussing on cystitis and polynephritis because they are caused by the bacteria Escherichea coli (E. coli).

E. coli serve a positive purpose in the large intestine, where they break down the by-products of digestion. However, they are responsible for about eighty-five per cent of all urinary tract infections. E. coli, which enter through the perineum and travel through the urethra to the bladder, attach themselves to the cells in the bladder wall, where they reproduce, colonise and cause a bladder infection. Because this infectious process starts to destroy the superficial lining of the bladder and also disrupts the small capillaries, the urine of infected individuals often contains blood. If the infection progresses, the E. coli will then travel up the ureters and infect the kidneys.

Tamms-Horsfall glycoprotein, a natural substance present in the urine of some individuals, has the ability to attach itself to the E. coli bacteria and inhibit them from attaching to the bladder wall. Individuals with enough Tamms-Horsfall glycoprotein

are unlikely to get a urinary tract infection from E.coli. However, those who lack or have low levels of this natural substance are more susceptible.

In 1994, researchers at Weber State University in Utah, United States of America, discovered that cranberry contains a substance similar in activity to the Tamms-Horsfall glycoprotein. Much like natural glycoprotein, the substance can inhibit the attachment of E.coli to the bladder wall. In tests where cranberry was added to a petri dish along with E. coli bacteria and bladder cells, the addition of the cranberry substance kept the bacteria from attaching to the bladder cells.

Additionally, a 1994 Harvard University study involving 153 elderly women with histories of repeated urinary tract infections showed that regular consumption of cranberry juice cocktail can decrease the incidence of urinary tract infections. In a clinical trial conducted by Weber State University, the same conclusion was drawn using a concentrated cranberry product. The product, in dehydrated capsule form is equivalent to twelve to sixteen 6-ounce glasses of cranberry juice.

The human body does have natural barriers against urinary tract infection. In men, the urethra is up to 25 cm long with natural bends, both of which make it difficult for bacteria to reach the bladder.

In females, the perineum helps prevent bacteria from entering the urethra. Females are at a disadvantage, however, because the perineum can be damaged or irritated by tight clothing, intercourse, poor hygiene or bubble baths and thus allow bacteria to make their way into the bladder. In addition, the female urethra is only 5 cm long and straight, making it easy for bacteria to reach the bladder. If a female infant or young girl has two or three bladder infections, X-rays are in order to rule out possible anatomical abnormalities. In the case of young boys, X-rays are in order with the first infection to ascertain whether the urinary tract is intact and functioning properly.

Females are more likely than males to get a second urinary tract infection, and within as little as two weeks of the first flare-up. During the initial infection, the lining of the bladder is injured, making it more susceptible to new E.coli seeking to attach themselves before the lining has a chance to heal.

Currently, the only alternative to cranberry for preventing urinary tract infections is to take an antibiotic regularly. This practice is not a good solution because of the risk of allergic reactions and also of developing a strain of bacteria resistant to antibiotics. On the other hand, the risk of allergic reactions to cranberry is negligible and the bacteria have not been shown to be resistant to it.

Cranberry may also be effective for patients who have difficulty emptying their bladder, such as men with enlarged prostrates or patients with neurological abnormalities including stroke or spina bifida. When urine remains in the bladder, bacteria have a greater chance of attaching to the bladder lining. Individuals with catheters also face an increased risk because bacteria can be introduced any time a foreign object enters the bladder.

EXAMPLE

The following is a typical example of a cranberry fruit extract effervescent tablet formulation:

Ingredient	Weight (mg)
Citric Acid	1100
Calcium Carbonate	200
Polydimethylsiloxane	20
Sodium Bicarbonate	800
Cranberry 25:1 Fruit Extract	200

Lactose	1451
Sucralose	9
Blackcurrant Flavour, Powdered	50
Polyvinylpyrrolidone	40
Polyethylene Glycol 6000	60
Fumaric Acid	70
Quantity per tablet	4000

The method or process of manufacture is as follows:

- The effervescent acid is loaded into the mixing bowl of a granulating machine fitted with a two-speed planetary mixing blade and with a separate horizontally mounted high speed chopper mixer. The polydimethylsiloxane is added and the conventional mixing blade is switched on, with high speed being selected. Mixing is continued until all of the acid has been coated with this material and a damp, solid mass is formed. After this has been achieved, the chopper mixer is switched on and the mass is subjected to this treatment for about 0.5 to 1.0 minutes, followed by a further 2 to 5 minutes of high speed mixing by the planetary blade.

- The mixture is then discharged onto stainless steel trays in thin layers. These trays are loaded into a drying oven pre-heated to and set at 50°C for about 18 hours to dry.

- According to one embodiment using citric acid and a Karl Fischer Titrator apparatus, the maximum water content of the dried, coated citric acid is 0.2% w/w.

- The dried, coated acid is then loaded into a mixing machine where it is blended with the other ingredients of the formula. The mixing time is about 3 to 5 minutes.

- The mixture is compressed into tablets using a Jenn-Chiang Model JC-SH-31 pre-compression type tableting machine, to the following specifications:

Tablet Diameter	:	25.4 mm
Tablet Shape	:	Round, Flat, with bevelled edges
Tablet Weight	:	4000 mg+/-100mg.
Machine Speed	:	14-19 rpm
Machine Pressure	:	8 – 11 Kpa/sq.cm.

Packs of tablets stored at 30°C were examined at three-monthly intervals, and after 18 months, no degradation in terms of appearance, average individual tablet weights and disintegration time was observed.

c) **Effervescent Glucosamine Tablets**

Glucosamine may provide assistance in the management of osteoarthritis, by stimulating the production of cartilage replacement components and joint lubricants.

Articular cartilage is the smooth, tough, rubbery and gelatinous material surrounding the joints of the human body. Cartilage acts as a shock absorber, stopping the ends of the joints from rubbing together. In people with osteoarthritis, wear and tear causes the cartilage to break down and dry out, lose its springiness, crack and, in some cases, disappear, leaving the ends of the bones exposed.

With no known cure for osteoarthritis, conventional treatment required the use of pain killers such as paracetamol, aspirin or powerful non-steroidal anti-inflammatory drugs

(NSAIDS) such as ibuprofen. When drugs no longer mask the pain, surgery replaced the affected joint. But this practice has begun to change, with the use of glucosamine. Researchers have found that it helps reduce the pain of osteoarthritis, stimulating the growth of new cartilage to such an extent that it stems the progression of the disease and in some cases, actually reverses it.

Glucosamine is a naturally produced building block for the body's natural synthesis of synovial fluid and articular cartilage. It is a precursor to the generation of glycosaminoglycans and makes up 50% of the composition of hyaluronic acid, both of which are key components in the biosynthesis of very large molecules called proteoglycans and collagen. Proteoglycans are the natural lubricants and shock absorbers found in joint cartilage and the surrounding joint fluid.

Glucosamine is an amino disaccharide which the body makes from glucose. It is found in all of the tissues of the body but occurs in especially high concentrations in cartilage, tendons and ligaments. Its main function appears to be to stimulate the manufacture of long chains of sugars called glycosaminoglycans, which comprise the bulk of cartilage tissue. However, the rate of manufacture of glucosamine by the body is limited, which is why people who put stress on their joints can experience stiffness, inflammation and even sustain injury. As we age, the rate of generation of glucosamine by the body decreases, which can lead to lower concentrations in cartilage, which then become thinner and form the start of osteoarthritis.

The onset of osteoarthritis can be very subtle. As the cartilage thins and then disappears, the bones in the joint scrape against one another and form bone spurs. Symptoms typically begin with morning joint stiffness, occasional pain in the affected area and reduced mobility. Over time, the condition progresses from one joint to another, mainly in the weight-bearing joints of the hips, knees, spine and also in the fingers.

German doctors in the 1960s were amongst the first to use glucosamine (as an injection) to treat osteoarthritis patients. Later, an Italian pharmaceutical company developed glucosamine sulphate tablets for use in clinical studies using glucosamine orally for 20 patients with osteoarthritis in their knees. Half of the patients were given 500 mg three times a day, the other 10 patients were given a placebo. Those patients who received glucosamine tablets reported significantly reduced pain, joint tenderness and swelling and improved mobility, more quickly than those taking the placebo tablets. Even when the placebo tablets were replaced with Ibuprofen tablets, glucosamine was more effective in reducing pain and improving joint function.

One study found that glucosamine rebuilt cartilage and actually reversed deterioration. This result flew in the face of the conventional view that osteoarthritis cannot be arrested, let alone reversed.

The patients using glucosamine had none of the side-effects of conventional pain-killing drugs. Only rarely have people taking glucosamine reported stomach upsets or nausea. Approximately 25% of people using NSAIDS for pain relief develop stomach ulcers. Another little known side effect is the destruction and inhibition of the body's ability to maintain cartilage. This makes the condition worse in the long term.

Glucosamine targets the underlying cause of the condition rather than treating the symptom – pain. It helps to restore the thick, gelatinous shock-absorbing fluids around the joints and between the vertebrae and prevents the cartilage from breaking down. It also has some anti-inflammatory properties.

Glucosamine is mainly used to treat osteoarthritis. In some parts of Europe, it has replaced anti-inflammatory drugs as the first-line treatment. However, glucosamine does not yield quick results. It takes longer to show results than NSAIDS, typically weeks or even months, compared to hours, but the benefits are generally longer lasting.

Glucosamine is also used by athletes and those who exercise regularly – either to help with specific injuries – or for treating sore joints and muscles. Back problems such as slipped discs and sciatica have been helped by taking glucosamine. It also aids wound and scar healing. Research has shown that it can help IBS and digestive tract complaints such as ulcerative colitis and Crohn's disease.

In this case, a substance from the glucosamine coats the mucous membranes of the digestive, respiratory and genito-urinary tracts, creating a protective barrier against a host of irritants, and, since 1992, veterinary surgeons have used glucosamine to treat arthritis in pets, farm animals and racehorses. Increasingly, glucosamine is being used preventively to guard against future joint and muscle problems.

Effervescent Glucosamine Tablets

Effervescent tablets are designed to be dissolved in a glass of water before ingestion, in contrast to swallowing them whole. If the active ingredient(s) in the effervescent tablet is soluble in water, absorption of the active ingredient by the body is much more rapid than the same active ingredient(s) in a conventional tablet. In the latter case, the tablet must disintegrate before the active ingredient(s) can dissolve in the gastric fluids, thus making them available for absorption into the body.

Effervescence is achieved by including one or more weak acids, for example citric acid or tartaric acid, and one or more effervescing alkalis, for example, sodium bicarbonate, potassium bicarbonate or calcium carbonate, in the formula. In the presence of traces of water, reaction takes place between these ingredients, liberating carbon dioxide, the "effervescence". Also, water is generated by this reaction which then continues until all of one or both of these ingredients have reacted.

As the glucosamine complex (D-glucosamine sulphate.2 KCl) included in the formulation is soluble in water, all ingredients in the formulation have been dissolved in water before ingestion.

Generally, the amount of moisture in the atmosphere is sufficient to start this reaction unless precautions are taken to provide a barrier between the acid(s) and the alkali(s) in each tablet during manufacture, packaging and storage. To minimise this problem, it has been traditional practice to separately pre-dry all of the ingredients in an effervescent tablet formula to remove adsorbed moisture and then to continue the processes of mixing and compressing the powders into tablets in a controlled environment in which the relative humidity of the air is less than 10%.

The unique effervescent base used in these effervescent tablets according to this invention overcomes these limitations and enables these processes to be carried out in a normal or ambient environment.

Example of an Effervescent Glucosamine Tablet

The following is a typical effervescent glucosamine tablet formulation containing 500 mg of glucosamine sulphate complex. This formula utilises the unique effervescent tablet base, with variations in some of the excipients to provide a palatable drink.

Ingredient	Weight (mg)
Citric Acid	1000
Calcium Carbonate	100
Polydimethylsiloxane	20
Glucosamine Sulphate Complex	500
Polyvinylpyrrolidone	65

Sodium Bicarbonate	800
Lactose	1405
Orange Flavour Powder	75
Sucralose	10
Fumaric Acid	50
Polyethylene Glycol 6000	75
Quantity per tablet	4100

The method or process of manufacture is as follows:

- The effervescent acid is loaded into the mixing bowl of a granulating machine with a two-speed planetary mixing blade and with a separate horizontally mounted high speed chopper mixer. The polydimethylsiloxane is added and the conventional mixing blade is switched on, with high speed being selected. Mixing is continued until all of the acid has been coated with this material and a damp, solid mass is formed. After this has been achieved, the chopper mixer is switched on for about 0.5 to 1.0 minutes, followed by a further 2 to 5 minutes of high speed mixing by the planetary blade.

- The mixture is then discharged onto stainless steel trays in thin layers. These trays are then loaded into a dry oven pre-heated to and set at 50 degrees Celsius.

- According to one embodiment using citric acid and a Karl Fischer Titrator apparatus, the maximum water content of the dried, coated acid is 0.1%.

- The dried, coated citric acid is then loaded into the mixing machine where it is blended with the other ingredients of the formula. The mixing time is about 3 to 5 minutes.

- The mixture is compressed into tablets using a Jenn-Chiang Model JC-SH-32 pre-compression type tableting machine to the following specifications:

Tablet Diameter	:	25.4 mm
Tablet Shape	:	Round, Flat, with bevelled edges
Tablet Weight	:	4100 mg+/-100mg.
Machine Speed	:	14-19 rpm
Machine Pressure	:	8 – 11 Kpa/sq.cm.

The tablets so produced were subjected to stability testing similar to that described above, and showed that the tablets were physically stable over a period of 18 months.

d) Effervescent Ubidecarenone and Carnitine Tablets

(i) **<u>Ubidecarenone</u>**

This substance is usually referred to as Co-Enzyme Q 10 or CoQ10. It is a naturally occurring Ubiquinone (Co-Enzyme Q (n), where n may vary from 1 to 12. For ubidecarenone, n=10).

Co-Enzyme Q 10 has been called "The Miracle Nutrient" because of its ubiquitous health and therapeutic benefits. It is a natural nutrient that is essential to the health and vitality of every cell in the human mammalian body. It is necessary for cellular respiration, for regulation of the production of energy (ATP), the generation of new cells and the repair of damaged cell tissue. Co-Enzyme Q 10 is also both a powerful oxidant and an anti-oxidant. It is a fat soluble, super anti-oxidant supplement, the actions of which in the body and its chemical structure, resemble those of Vitamin E and Vitamin K.

It is found in all mitochondria. It participates in the manufacture of adenosine triphosphate (ATP), a universal energy storage molecule throughout the body. CoQ10 is an essential nutrient that is said to supply the biochemical "spark" that creates cellular energy.

CoQ10 promotes good health by supporting intrinsic body systems responsible for producing energy. It acts as a 'shuttle' for electrons involved in the creation of energy producing enzymes. Human bodies cannot survive without it. If body levels of CoQ10 start dropping, so does the general health of the individual. Scientists estimate that once levels drop below the 25% deficient levels, many disease states can begin to flourish.

As indicated above, it is a naturally occurring nutrient present in every cell in the body and is also present in and is available from certain foods, especially fish and meats, particularly organ meats. The body generates its own CoQ10, but many people probably do not make it in sufficient quantities because of the complicated biochemical processes required for its production.

As we age, the body loses its efficiency in manufacturing important nutrients. In addition, people with serious diseases, such as heart disease and cancer, tend to have low CoQ10 levels. Hence even though the young may be able to get enough CoQ10 by making it and ingesting it through their diet, a gradual deficiency may develop as we reach middle age and older. Thus, supplementation can prove very beneficial.

This important nutrient plays two major roles in the body. Firstly, CoQ10 helps in the energy production within each cell. The body, just like a car, needs fuel. Our primary source of fuel is through fats, proteins and carbohydrates in the diet. After digestion in the stomach, the nutrients from foodstuffs are absorbed into the bloodstream and circulate to various tissues

and cells. The cells have to break down the sugars, fats and amino-acids into a form that makes energy. This energy production occurs in organelles, or microscopic organ-like structures called mitochondria and CoQ10 plays a key role in this activity.

There are hundreds, sometimes thousands, of mitochondria within each cell. In a sense, they are the factories of the cells, with the final product being energy. The energy that is produced is stored in ATP. It is carried by electrons and protons, which are subatomic particles. Numerous compounds are responsible for moving these energetic electrons and protons around in the cells. CoQ10 is one of these compounds. Others include the B-group vitamins and alpha lipoic acid.

CoQ10 also serves as an anti-oxidant, which is the second role. By controlling the movement of electrons, CoQ10 limits the production of dangerous free radicals, which are molecules lacking one electron in what should be a pair.

Research and the clinical practice of some physicians have shown CoQ10 to be helpful in treating a number of conditions. Among these are congestive heart failure, coronary artery disease. CoQ10 may be applicable even in cases of previous heart attacks and for those about to undergo heart surgery. High cholesterol levels, high blood pressure (hypertension), breast cancer and fatigue are further conditions where supplemental doses of CoQ10 may be helpful.

CoQ10 has been studied most thoroughly for its roles in maintaining normal heart function and preventing serious disease. Heart muscle is constantly using energy to pump blood through the body. CoQ10 helps in that energy production. Dozens of well-designed and performed human trials have been

published in the scientific literature regarding the heart energising benefits of this nutrient.

In Japan, more than 12 million people take daily doses of CoQ10 prescribed by their physicians as the "medication of choice" for prevention and treatment of heart and circulatory diseases. Hundreds of papers extolling the benefits of CoQ10 have been published in Japan, the Soviet Union, Europe and, more recently, the USA. Researchers at the Free University in Brussels have demonstrated that CoQ10 boosts the performance of the heart, even after cardiac disease has reached a severe stage. A combined study between the Centre for Adult Diseases in Osaka, Japan and the University of Texas found that CoQ10 had the ability to lower blood pressure. Additional studies indicate that CoQ10 has been shown to be a potent anti-oxidant and as an immunologic stimulant.

CoQ10 is present in all body cells. The major portion of cellular CoQ10 is present in the mitochondria as part of the electron transport system. It is in this system that oxidative phosphorylation, a critical link to life itself, and the rate of oxidation of nutrients is regulated. Thus, the heart and the liver, which are both central to this process, contain the largest number of mitochondria per cell and the greatest amount of CoQ10.

CoQ10 may be of benefit in the prevention of cardiovascular disease. In the heart, cellular mitochondria provide energy for the intake of nutrients and to support its constant pumping action. The heart muscle utilises triglycerides prepared by the liver as fuel to generate its energy; thus the heart is dependent on motochondrial phosphorylation to generate the energy needed for its non-stop operation.

Because the heart is so metabolically active and needs a constant supply of usable fuel for its constant contraction and pumping action, it may be susceptible to any effects resulting from a deficiency of CoQ10.

CoQ10 has been shown to be a supplement of great promise in the treatment of heart disease. When CoQ10 was administered to heart patients orally as a dietary supplement, failing cardiac systems took on renewed vigour. The main parameters of measurement for heart efficiency, namely cardiac output and stroke volume, were significantly increased. This indicated that the organ had taken a turn towards better health, as opposed to continuation of a degenerative disease situation.

CoQ10 is found in every cell of the body. The body extracts its energy from carbohydrates, fats and protein consumed in the diet or stored in the body. This energy is harnessed for one major purpose, to combine adenosine and phosphate to form the energy-rich compound ATP. ATP serves as the energy current for all cells and as it is not stored within the body, it must be constantly synthesised to provide a continuous supply of energy. The foods we eat and which are stored within the body provide the starting materials for making ATP, with the help of CoQ10. CoQ10 is the key to the process that produces 95% of the cellular energy in our bodies. It is considered that without the CoQ10, the human body would not have the energy to stay alive.

Many of the ill effects of aging can be linked directly to the reduction in the performance of the body's immune system. It is considered to be not just a coincidence that when the body is unable to generate all of the CoQ10 it needs, aging may be observed. For example, in studies in both Japan and the USA, physicians have observed lowered blood pressures in cardiac high risk patients by simply adding CoQ10 supplements to their diets. Further, clinical

trials involving athletes have demonstrated that regular supplementation with CoQ10 may enhance aerobic ability and muscle performance.

It has also been observed that relief from Chronic Fatigue Syndrome (CFS) may be achieved when regular supplements of CoQ10 are taken, even when it appears that persons suffering CFS are not deficient in this nutrient. Taking extra CoQ10 prompts the body to improve the performance of the partner enzyme it reacts with to convert food into energy.

(ii) **Carnitine**

Carnitine is an amino-acid that can be synthesised by the liver provided adequate supplies of the building blocks – lysine, thiamine hydrochloride (Vitamin B1), pyridoxine hydrochloride (Vitamin B6) and iron are available. Provided a balanced diet is regularly taken, these can usually be derived from muscle and organ meat, fish and dairy products.

It is made from two other amino-acids, namely methionine and lysine and has been shown to have a major role in the metabolism of fat and in the reduction of triglycerides because of this action. It works by increasing the utilisation of fats. It transfers fatty acids across the membranes of the mitochondria where they can be utilised as sources of energy. It also increases the rate at which the liver uses fats. By preventing fat build-up, this amino-acid assists in weight loss and the risk of heart disease.

Carnitine has been shown to be deficient in the hearts of people who have died of acute myocardial infarction. It has recently been found that supplements of this substance improve exercise tolerance in people with angina, possibly by increasing the ability to utilise fatty acids for energy. Supplementation may also help in mitral valve prolapse and in immune system depression.

Muscular dystrophy and myotonic dystrophy have been shown to lead to carnitine loss in the urine and therefore the desirability of supplementary doses to maintain an adequate supply in the body.

Carnitine was also found to block atrial fibrillation after initial atropine administration about as well as quinidine, without many of quinidine's side effects.

Because of its role in transforming fatty acids into energy and its main dietary sources, vegetarians are more likely to be deficient in carnitine because they do not eat meat. Their diets are often low in lysine, also.

Carnitine is stored primarily in the skeletal muscles and heart, where it is needed to transform fatty acids into energy for muscular activity. It is also concentrated in sperm and the brain. Many athletes have noted increased endurance and muscle building with carnitine supplementation. L-carnitine has been recommended in the treatment of ischaemic heart disease and Type IV hyperlipidemia. Carnitine has been shown to be beneficial for other heart problems such as angina, arrhythmia as well as poor endurance, muscle weakness or obesity.

In the object of this patent, Carnitine is formulated in combination with CoQ10 as the active ingredients of this effervescent tablet dosage form. This dosage form provides these active ingredients as a solution in water, which is available for more rapid absorption than in a conventional tablet.

EXAMPLE

A typical effervescent tablet formulation including CoQ10 and carnitine fumarate, a salt formed by a reaction between an A-carnitine salt and fumaric acid.

Ingredient	Weight (mg)
Citric Acid	1100
Calcium Carbonate	100
Polydimethylsiloxane	15
Sodium Bicarbonate	800
Lactose	1320
Riboflavine 5-Phosphate Sodium	15
L-carnitine Fumarate	431
CoQ10	30
Sucralose	20
Vanilla Powder Flavour	20
Lime Powder Flavour	40
Lemon Powder Flavour	40
Polyvinylpyrrolidone	40
Fumaric Acid	54
Polyethylene Glycol 6000	75
Fumaric Acid	50
Weight per tablet	4100

Note: The Riboflavine 5-Phosphate Sodium is present as a colouring agent, but may also provide a source of Vitamin B2. 15 mg of this substance is equivalent to 10 mg of Vitamin B2, with a 10% average.

The method or process of manufacture of this effervescent tablet product is similar to that specified for Cranberry effervescent tablets and glucosamine effervescent tablets, with the different active ingredients.

The tablets so produced were subjected to stability testing similar to that described above, and confirmed the on-going stability of the formulation and also the potency of the active ingredient.

The formulae and processing procedures according to the present invention permit the manufacture, storage and packaging of effervescent tablets containing Cranberry or other dietary or therapeutic substances of natural origin in a manufacturing environment where the temperature but no the relative humidity of the air is controlled. As a result, the cost of both the initial investment and operations in processing and packaging are significantly reduced. Still further savings in the costs of packaging are achievable because it is not necessary to individually wrap each such tablet for protection. The effervescent tablets so produced allow for fast absorption of the active ingredients from the stomach for immediate beneficial dietary or therapeutic effect.

Although non-limiting exemplary embodiments of the present invention have been shown and described, it will be apparent to those having ordinary skill in the art that a number of changes, modifications or alterations to the invention described herein may be made, none of which depart from the spirit of the present invention. All such changes, modifications, and alterations should therefore be seen as being within the scope of the present invention.

It should be appreciated that the present invention provides a substantial advance in the manufacture and storage of effervescent tablets containing dietary and therapeutic substances of natural origin, providing all of the herein-described advantages without incurring any relative disadvantages.

The term "comprising", as used herein, is used in the inclusive sense of "having" or "including", and not in the exclusive sense of "consisting only of".

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. An effervescent tablet base composition comprising at least one acid and at least one effervescing alkalis, wherein the acid component is pre-coated with a protective layer of a polydimethylsiloxane to substantially minimise contact between the acid and atmospheric moisture.

2. An effervescent tablet base composition according to claim 1, wherein said acid is citric acid or tartaric acid.

3. An effervescent tablet base composition according to claim 1 or claim 2, wherein said alkali is selected from the group comprising sodium bicarbonate, potassium bicarbonate and calcium carbonate.

4. An effervescent tablet base composition according to any one of claims 1 to 3, wherein the pH of the polydimethylsiloxane is similar to the pH of the acid component.

5. An effervescent tablet base composition according to claim 4, wherein the pH of the polydimethylsiloxane is in the range of about 2-3.

6. An effervescent tablet base composition according to any one of claims 1 to 5, wherein the concentration of the polydimethylsiloxane varies in the range of about 0.05% to about 1.5% of the total weight of the composition.

7. An effervescent composition comprising a tablet-base according to any one of claims 1 to 6, together with a cranberry fruit extract.

8. An effervescent composition comprising a tablet-base according to any one of claims 1 to 6, together with a glucosamine salt.

9. An effervescent composition comprising a tablet-base according to any one of claims 1 to 6, together with Co-Enzyme Q10 and Carnitine.

10. An effervescent composition as claimed in any one of claims 1 to 9, compressed into tablet form.

11. An effervescent composition as claimed in any one of claims 1 to 10, wherein said effervescent composition is used as a dietary supplement or for medicinal or therapeutic purposes.

12. An effervescent composition substantially as herein described and exemplified.

13. A method for preparing an effervescent composition of the type defined in any one of claims 1 to 11, wherein at least one acid and/or at least one other effervescing component of said composition is pre-coated with polydimethylsiloxane before the pre-coated component(s) is further mixed with the remaining ingredients of said composition.

14. A method for preparing an effervescent composition substantially as hereinbefore described and exemplified.

15. An effervescent composition when prepared according to the method as claimed in claim 13 or claim 14.

Dated this 3rd day of August 2001

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